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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/819,464 | 03/28/2001 | Martin Friede | B45070-1 | 1150 |

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| EXAMINER | |
|---|---|
| LUCAS, ZACHARIAH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1648 | |

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/819,464 | FRIEDE ET AL. | |
| | Examiner | Art Unit | |
| | Zachariah Lucas | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *47,48 and 50-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47,48 and 50-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8-23-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. In the prior action, mailed on April 22, 2004, claims 1-49 were pending in the application, with claims 47 and 48 under consideration and rejected, and claims 1-46, and 49 withdrawn as to non-elected inventions. In the Response filed on July 16, 2004, the Applicant amended claims 47 and 48, cancelled claims 1-46, and 49, and added new claims 50-73.

2. Currently, claims 47, 48, and 50-73 are pending and under consideration in the application.

### *Priority*

3. Applicant's submission of a petition for a delayed claim of priority on January 13, 2004 is noted and a copy of the United Kingdom priority application GB 9513107.4. The petition was granted in a letter mailed on August 17, 2004.

### *Information Disclosure Statement*

4. The information disclosure statement (IDS) submitted on August 23, 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

5. It is noted that the Kensil et al. patent (U S 5,057,540) has been crossed out on the IDS. This is because the reference was previously made of record and considered in the IDS of January 2004.

### *Claim Objections*

6. **(New Objection-Necessitated by Amendment)** Claims 62, 63, 70, and 71 are objected to because of the following informalities: these claims refer to a compound (3D-MPL) by its complete name (3 De-O-acylated monophosphoryl lipid A). Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. **(Prior Rejection- Withdrawn)** Claims 47 and 48 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on methods of stabilizing or reducing the reactogenicity of the saponin QS-21 by adding an "excess of sterol to the adjuvant formulation." The claims are rejected because the Applicant has indicated that the term "excess" is intended by Applicant to include embodiments wherein the sterol and adjuvant are present in *equal* amounts. Thus, the term as used by the Applicant is contrary with the way the term is used in the art. However, it is also noted that the MPEP (8$^{th}$ Ed., May 2004 revision) states "a patentee may use terms in a manner contrary to or inconsistent with one or more of their ordinary meanings if the written description clearly redefines the terms." Section 2173.05(a) III. In view of the revised MPEP, and the presence of language in the specification clearly pointing out that the Applicant intended the term "excess" to include embodiments wherein QS-21 and sterol were present in equal amounts (e.g., page 5, lines 29-35), the rejection is withdrawn.

9. **(Prior Rejection- Maintained in part)** Claims 47 and 48 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is extended to new claims 56, 57, and 62-73 for the reasons of record. As indicated above, the claims read on a method comprising the addition to a QS21 containing adjuvant formulation an excess of a sterol. In particular, the claims read that the methods include the "addition of excess sterol to the adjuvant formulation (weight/weight)." The claims were rejected for two reasons.

First, it was unclear what the importance of the parenthetical phrase "weight/weight" was to the claim. In view of the amendments to the claim, clarifying that the determination of an "excess" of sterol is based on the weight of the components, the first ground of rejection is withdrawn.

Second, the claim was rejected because it was unclear if the determination of the excess is based upon the comparative weights of the saponin and the sterol, or upon the weights of the saponin and the formulation containing the saponin. The dependent claims and the Applicant's assertions in the Response, indicate that the latter is the case. However, the independent claims indicate the former. While the Applicant has stated that the QS21 is in substantially purified form, this does not exclude the presence of other components in the adjuvant formulation that would not be found in the Quil A formulation from which QS21 may be derived- e.g., the presence of pharmaceutical carriers, detergents, or other adjuvants. Thus, the insertion of the phrase into the claim does not resolve the indefiniteness. It is suggested that the claims be amended to read on methods wherein - - an excess by weight of sterol is added to the adjuvant formulation, wherein the excess is based on the ration of sterol to QS21- - or similar language.

### *Claim Rejections - 35 USC § 102*

10. **(Prior Rejections- Withdrawn)** Claims 47 and 48 were rejected under 35 U.S.C. 102(b) in the prior action as being anticipated by the teachings of Lipford et al. (Vaccine 12(1): 72-80, of record in the March 2001 IDS) in light of the teachings of Kensil et al. (U.S. Patent 5,583,112), and by as being anticipated by Mackenzie et al. (EP 0415794) in light of the teachings of Kensil. In the Response, the Applicant amended the claims to read on compositions wherein the QS21is present in substantially purified form. The Applicant argues that this amendment distinguishes the claimed compositions from those of the cited art. This argument is found persuasive. The rejections are therefore withdrawn.

### *Claim Rejections - 35 USC § 103*

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. **(Prior Rejection- Maintained)** Claims 47 and 48 rejected under 35 U.S.C. 103(a) as being unpatentable over Lipford in view of the teachings of Kensil. The Applicant traverses the rejection on the grounds that the references cited do not provide motivation for the combination of the two references, and in particular, do not teach or suggest that the use of the cholesterol containing liposomes of Lipford would reduce the reactogenicity or hydrolysis of the QS-21

adjuvant described in Kensil. These arguments are not found persuasive. The rejection is therefore maintained against claims 47 and 48, and extended to new claims 50, 51, 56-59, 64-69, 72, and 73.

The Applicant argues that the Examiner has alleged that those in the art would combine the indicated prior art references on the grounds that such a combination would result in the reduced reactogenicity or hydrolysis of the QS-21. This is not an accurate assessment of the rejection. The Examiner did not assert that it would be obvious to those in the art to combine the references such that the benefits identified in the claims would be achieved. Rather, the Examiner stated that the art rendered obvious the combination, and that such a combination would result in the performance of the claimed methods. The reduced reactogenicity and hydrolysis would be inherent in the making of the QS-21 containing liposomes suggested by the Kensil/Lipford combination. The Applicant has therefore done no more than recognize a previously unrecognized additional advantage of the combination. See, MPEP § 2145 II. The fact that the Applicant identified such a latent property does not render the claims non-obvious.

The rejection is that the combined teachings of Lipford and Kensil render obvious the inclusion of QS-21, rather than Quil A, into the saponin-liposomes described by Lipford. The basis for this is that Kensil discloses that QS-21, which is also purified from Quil A, is an obvious substitute for Quil A. The reference teaches that QS-21 has adjuvant effects equal to or greater than Quil A. Columns 6, and 22-23. In particular, the patent teaches that the purified saponins of the patent (including QS-21) showed adjuvant effects at lower dosages than the crude saponin extract (Quil A). Columns 3-4, and col. 6, lines 30-40. Further, the reference teaches that these purified saponins tend to be less toxin (have less hemolytic activity) than the

Quil A extract. Columns 3-4, and column 20. Thus, the art provides several reasons for the substitution of QS-21 for Quil A in the compositions of Lipford.

Further, it is not clear that the reduced hydrolysis of the saponin adjuvants by incorporation of the adjuvant into liposomes would not have been recognized by those in the art. For example, it is known in the art that incorporation of compounds into sterol containing liposomes protects the encapsulated compounds from hydrolysis. See e.g., Nacucchio et al., Antimicrob Agents and Chemother 27:137-39 (teaching the encapsulation of certain drugs in cholesterol containing liposomes protects the drugs from hydrolysis). In view of these teachings, those in the art would have expected a reduced incidence of hydrolysis of compounds, including the saponin adjuvants of Kensil, incorporated into such liposomes.

For the reasons above, the Applicant's arguments in traversal are not found persuasive.

Claims 64-69 further limit the claimed method to embodiments wherein the sterol and QS-21 form into unilamellular liposomes, and to embodiments wherein the adjuvant formulation additionally includes alum salts. The liposomes are rendered obvious by the combined teachings of Kensil and Lipford as described above. Kensil additionally teaches that other adjuvants, including alum may be used with the saponin adjuvants. Column 8, lines 25-46. It would therefore have been obvious to include such adjuvants with the QS-21 in the liposomes suggested by Kensil and Lipford.

The rejection is therefore maintained and extended for the reasons above, and the reasons of record.

13. **(New Rejection-Necessitated by Amendment)** Claims 52-55, 60, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Lipford in view of Kensil as applied to claims 47, 48, 50, 51, 56-59, 64-69, 72, and 73 above, and further in view of Bonati et al. (U.S. Patent 4,101,652- of record in the IDS of March 2001). These claims further limit the methods to embodiments wherein the QS21 to sterol ratio is either 1:2 or 1:5 weight/weight. The teachings of Lipford and Kensil have been described above. Kensil does not appear to teach a preferred weight ratio range of sterol to saponin. Further, the teachings of Bonati state that, in a composition comprising complexes of sterol to saponins, "the weight ration between the saponin and the sterol is not unduly critical." Thus, the ration of sterol and saponin appear to be determined by obvious optimization of the suggested inventions.

Further, the art also provides some indication that an excess of sterol in the presence of a saponin would reduce the reactogenicity of the adjuvant composition. See, Scott et al., Int Archs Allergy Appl Immun 77: 409-12 (indicating that excess sterol containing liposomes, while reducing inflammatory action of saponins, did not affect adjuvant activity). Thus, there is adequate motivation to use, and there would have been a reasonable expectation of success in the use of, excess sterol in the adjuvant compositions.

14. **(New Rejection-Necessitated by Amendment)** Claims 62, 63, 70, and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Lipford in view of Kensil as applied to claims 47, 48, 50, 51, 56-59, 64-69, 72, and 73 above, and further in view of Prieels et al. (WO 94/00153- of record in the August 2004 IDS). These claims describe the methods of claims 47 and 48 wherein the adjuvant formulation also comprises alum salts and/or 3 De-O-acylated

monophosphoryl lipid A (3D-MPL). Lipford and Kensil teach the methods of claims 47 and 48. However, while Kensil indicates that the saponins disclosed therein may be used with other adjuvants, the reference does not specifically suggest the use of 3D-MPL.

However, the teachings of the Prieels reference demonstrate a synergy in the use of both QS-21 and 3D-MPL as adjuvants. Whole document. Thus, from these teachings, it would have been obvious to those in the art to include 3D-MPL in the liposome formulations comprising QS-21 such that the known synergistic activities could be used.

***Conclusion***

15. No claims are allowed.

16. The following prior art reference is made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Takechi et al., Planta Med 58: 128-30. This reference indicates that cholesterol interferes with the hemolytic activity of saponins. Thus, the reference indicates that the addition of cholesterol to a saponin adjuvant would have been expected to result in reduced reactogenicity (hemolysis).

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

JAMES HOUSEL 9/20/04
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